PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



| Applicant's or agent's file reference<br>4-32514A/USN | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/EP 03/05762 | International filing date *(day/month/year)*<br>02.06.2003 | Priority date *(day/month/year)*<br>03.06.2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>A61K31/40 | | |
| Applicant<br>NOVARTIS AG | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 19.12.2003 | 23.09.2004 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office - P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk - Pays Bas<br>Tel. +31 70 340 - 2040 Tx: 31 651 epo nl<br>Fax: +31 70 340 - 3016 | Authorized Officer<br>van der Kooij, M<br>Telephone No. +31 70 340-4606 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/05762

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-22 as originally filed

**Claims, Numbers**

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1, 4-6 and 8-17 (all partially)

   because:

   ☒ the said international application, or the said claims Nos. 1 (and 5-7 as far as depending on claim 1) and 8-9 (and 11-17 as far as depending on 8 and 9) (all with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 4-6 and 8-17 (all partially) are so unclear that no meaningful opinion could be formed *(specify)*:

   **see separate sheet**

   ☒ the claims, or said claims Nos. 4-6 and 8-17 (all partially) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 9-17 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 4 and 8-17 |
| | No: | Claims | 1-3 and 5-7 |
| Inventive step (IS) | Yes: | Claims | 4 |
| | No: | Claims | 1-3, 5-7 and 8-17 |
| Industrial applicability (IA) | Yes: | Claims | (see seperate sheet) |
| | No: | Claims | |

2. Citations and explanations

   **see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

***III.1). Rule 67.1(iv) PCT and Article 34(4)(a)(I) PCT.***

Claims 1, 8 and 9 (and claims 5-7 as far as dependent on claim 1, and 11-17 as far as dependent on claims 8 or 9) relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

***III.2). Articles 5 and 6 PCT.***

This application does not meet the requirements of Article 5 and 6 PCT, because claims 4-6 and 8-17 are not clear, nor sufficiently supported and the invention is not sufficiently disclosed by the description.

***III.2.1).*** Present claims 9-10 (and 11-17 as far as depending on them) relate to the treatment of a disease which actually is not well defined. The use of the definition "lowering LDL, Lp(a) and/or VLDL levels in a mammal" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to determine the disease for which protection might legitimately be sought.

***III.2.2).*** Present claims 4-6, 8-13 and 17 relate to a combination which are not defined at all (claims 8-11, 13 and 17: "another active agent") or defined by reference to desirable characteristics or properties, namely "an antihyperlipidemic agent", "a plasma HDL-raising agent", "an antihypercholesterolemic agent", "a cholesterol biosynthesis inhibitor", "an HMG-CoA reductase inhibitor", "an HMG-CoA synthase inhibitor", "a squalene epoxidase inhibitor", "a squalene synthetase inhibitor", "an ACAT inhibitor", "a cholesterol absorption inhibitor", " a bile acid sequestrant anion exchange resin", " an LDL receptor inducer", a cholesterol absorption inhibitor", "fibrates", "antioxidant vitamins", "a ß-blocker", an angiotensin II receptor (AT1) antagonist", "an angiotensin-converting enzyme inhibitor", "a renin inhibitor", "a platelet aggregation inhibitor", "a fibrinogen receptor antagonist" and "a glycoprotein IIb/IIIa fibrinogen receptor antagonist" (all claim 4-6 and 12).

The claims cover all combination preparations having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such combination preparations. In the present case, the claims so lack support, and the application so lacks disclosure.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An

attempt is made to define the combination by reference to a result to be achieved. Again, this results in a lack of clarity contrary to Article 6 PCT.
Only those parts of the combination preparation whereby probucol, nicotinic acid, niacinamide, vitamin B6, vitamin B12, vitamin B3, aspirin, ß-carotene, vitamin E, vitamin C, fluvastatin, lovastatin, pravastatin, atorvastatin and simvastatin (see claims 12 and 14-16) is characterized as second active component appear to be structurally defined, supported and disclosed.

***III.3). Rule 66.1(e) PCT.***

Only those parts relating to the use of compounds according to formula (I) for the treatment of the real and defined disease states mentioned in claims 1 and 7, i.e. hyperlipidemia and the following conditions associated with hyperlipidemia: atherosclerosis, angina pectoris, carotid artery disease, cerebral arteriosclerosis, xanthoma, CHD, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudification, myocardial infarction, dyslipidemia and post-prandial lipemia and appear to be clear, concise and sufficiently supported by the description. The examination will subsequently be prosecuted based on the specifically mentioned compounds and their claimed specific therapeutic use **(i.e. to matter for which an international search report has been drawn up (Rule 66.1(e) PCT)).**
In this respect, it has to be mentioned that a complete search was performed on the combination preparation as defined by claims 4, and 14-17, and will subsequently be examined without constraints.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

For the assessment of the present claims 1-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The Applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an

international search report has been drawn up, i.e. for the use of compounds according to formula (I) optionally in combination with other therapeutic agents as defined in claims 4 and 14-17 in relation to the treatment of the real and defined disease states mentioned in claims 1 and 7, i.e. hyperlipidemia, and the following conditions associated with hyperlipidemia: atherosclerosis, angina pectoris, carotid artery disease, cerebral arteriosclerosis, xanthoma, CHD, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudification, myocardial infarction, dyslipidemia and post-prandial lipemia.

***V.1). Prior art documents.***

Reference is made to the following documents:

D1: WO-A-0034241
D2: US6011155
D3: US6166063

The examination has been carried out assuming that the priority of the application is valid. However, the Applicant's attention is drawn to the fact that the documents which have been cited in the search report as "E" or "P" documents may become relevant in the national/regional examination phase.

***V.2). Article 33(2) PCT.***

Present claims do not meet the requirements of Article 33(1) PCT, because the subject-matter of claims 1-3 and 5-7 are not conform the criteria of novelty set forth by Article 33(2) PCT.

***V.2.1).*** D1 discloses the use of N-(substituted glycyl)-2-cyanopyrrolidines according to formula (I), including compound **1c** of the present application and pharmaceutically acceptable salts thereof (example 1; claim 4; page 1, paragraph 3) for treating conditions mediated by dipeptidyl peptidase-IV (DPP-IV) (page 1, paragraph 2; examples 2-12; claims 1-7). Also compositions comprising compounds according to formula (I) are described on page 17 paragraph 4-page 18, paragraph 1. In addition, it is expected that the compounds by virtue of their pharmacological activity are useful for "reducing mortality and morbidity after myocardial infarction" (page 7, paragraph 2). Myocardial infarction is commonly known to represent a condition associated with hyperlipidemia. The present application describes the conditions associated with hyperlipidemia in terms of *"reduction in necrosis **after** myocardial infarction"* (see claims 7 and 13). This comes down to treating myocardial infarction after the event happened

and includes also the prevention of dying in its broadest interpretation. For this reason, D1 is aimed to treat the same patients suffering from myocardial infarction.
Therefore, the novelty of claims 1-3 and 5-7 is anticipated by the disclosure of D1.
***V.2.2).*** Present claim 3 is drafted as composition claims with a first medical use linked to it. This manner of claiming is only allowable for a so-called "first medical use". Thus, any prior art document disclosing a composition comprising the specific compounds in relation to therapy is novelty destroying to present claim 1 (see D3). The therapeutic use in claim 3 is therefore not a limiting feature for the composition.
In this context, D2 is novelty destroying for the claim 1 as it discloses pharmaceutical compositions comprising compounds according to formula (I) (Examples 47, 49 and 53; claims 5, 9 and 10). Hence, D2 is relevant for the novelty of the subject-matter of claim 3.
***V.2.3).*** For similar reasons, D3 is equally relevant for the novelty of claim 3 because it describes tablet composition containing compound **1c** of the present application (column 16, lines 1-26 and claims 1-5).

***V.3). Article 33(3) PCT.***
Present claims do not meet the requirements of Article 33(1) PCT, because the subject-matter of claims 8-17 are not conform the criteria of the involvement of an inventive step as set forth by Article 33(3) PCT.
***V.3.1).*** Present claims 1-3 and 5-7 are not novel and consequently can not be regarded to fulfill the requirements of Article 33(3) PCT.
***V.3.2).*** Because the use of compounds according to formula (I) in relation to myocardial infarction is known (see D1), and the fact that the skilled person is aware of the known use of the second active ingredient as defined in claims 4, 12 or 14-16 in hyperlipidemic or associated diseases, the use of the combination preparation as defined in claims 8-17 can not be regarded as inventive. The use of a combination of two or more active ingredients which individually are already known to be useful in the same therapeutic application can only be regarded as inventive when a surprising effect can be assigned to the use of the combination. A synergistic effect *could* serve as such a surprising effect. In this respect, the application lacks supportive evidence that could account for the presence of a inventive step for the combination compounds according to formula (I) *and* the second active ingredient as defined in claims 4 or 12 or 14-16 in relation to modulating hyperlipidemia and/or conditions associated with hyperlipidemia.

***V.4). Article 33(4) PCT.***

***V.4.1).*** For the assessment of the present claims 1-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
***V.4.2).*** Claims relating to pharmaceutical compositions or combination preparations are generally considered as industrial applicable since they can be made or used in industry or agriculture. Therefore, claims 3 and 4 (and claims 5-7, 14-17 as far as depending on them) are considered to fulfill the requirements of Article 33(4) PCT.

***V.5). Further notes concerning form of claims:***
***V.5.1).*** Claims 5-6 and 14-17 should be construed as to depend on a single entity, i.e. either a product or a use (Article 84 EPC).
***V.5.2).*** Claim 17 does not contain any additional features which could restore novelty or inventive step of the preceeding claims en is therefore regarded as being superfluous (Article 84 EPC).

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